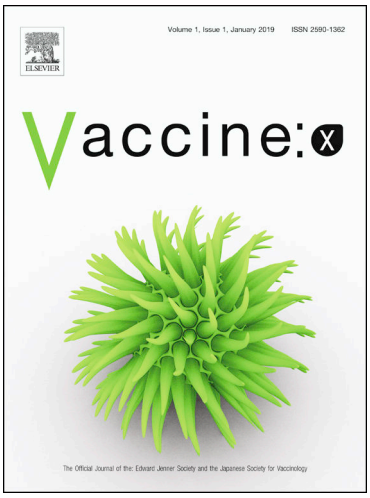
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Henoch-Schönlein purpura in a 6-year-old boy after initial COVID-19 vaccination

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Highlights

1. Henoch-Schönlein purpura onset after mRNA COVID-19 first vaccine dose in a child
2. Uncommon sign of a probable underlying autoimmune/inflammatory condition

3. Possibility of exacerbation following vaccination with a mRNA-based vaccine

Abstract

The COVID-19 pandemic has significantly impacted global health, and the widespread immunization of adults against SARS-CoV-2 has played a pivotal role in altering the course of the disease. While COVID-19 vaccine adverse events are generally uncommon and mild, the recent vaccination of the pediatric population has emphasized the need for vigilance and reporting of potential side effects. In this case report, we present a 6-year-old boy who developed Henoch-Schönlein purpura following the administration of the first dose of Pfizer-BioNTech BNT16B2b2 mRNA COVID-19 vaccine, making it the earliest reported case of such an adverse event. Our report highlights the importance of continued monitoring and reporting of adverse events in pediatric patients receiving the COVID-19 vaccine, as well as the need for prompt diagnosis and management of potential vaccine-related complications.

Keywords : mRNA COVID-19 vaccine, SARS-CoV-2, vasculitis

Introduction

As of March 10, 2023, the global mortality burden of COVID-19 was 6,881,955 (source: https://coronavirus.jhu.edu/map.html). Children and adolescents under 20 years of age accounted for only 0.4% of reported COVID-19 deaths (source: https://data.unicef.org/resources/covid-19-confirmed-cases-and-deaths-dashboard/). While children infected with SARS-CoV-2 rarely exhibit severe symptoms, between 1 and 5% of those infected may develop a mild form of COVID-19 disease [1], except for multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 [2], which can lead to severe disease and long-term side effects [3]. The COVID-19 pandemic has significantly impacted population health, even without acquired infection, and has challenged the resilience of health systems [4]. By March 10, 2023,

the worldwide administration of COVID-19 vaccine doses had reached 13,336,833,198 (source: https://coronavirus.jhu.edu/map.html) in a significant reduction in the spread of the virus, the prevention of severe illness and death, and ultimately contributing to herd immunity.

In December 2021, the Brazilian National Health Surveillance Agency (ANVISA) advised the administration of the Pfizer-BioNTech BNT16B2b2 mRNA COVID-19 vaccine in two doses of 10 micrograms each to children between 5 to 11 years of age, which is one-third of the dosage given to adolescents and adults. We report the earliest known occurrence of Henoch-Schönlein purpura in a 6-year-old boy following the first dose of the Pfizer-BioNTech BNT16B2b2 mRNA COVID-19 vaccine. Henoch-Schönlein purpura is a rare but significant disease that mainly affects children, causing symptoms such as palpable purpura, joint pain, abdominal discomfort, and kidney inflammation. Its underlying cause is immune complex-mediated small-vessel vasculitis, which highlights the importance of the immune system in its pathogenesis. Early diagnosis and management are crucial in preventing long-term complications and improving outcomes for patients affected by this condition. Importantly, episodes of Henoch-Schönlein purpura temporally associated with the administration of the COVID-19 vaccine in children are rare. While rare, reporting such cases is critical in ensuring the safety and efficacy of vaccines in children and providing timely and appropriate management for those affected.

Case Report

A five-month follow-up clinical investigation was conducted at a public tertiary pediatric hospital. The guardian consented to the publication of information and photographs. A 6-year-old boy was brought to the emergency department after developing palpable nonthrombocytopenic purpura in the buttocks and lower limbs that day (February 28, 2022) (Figure A). The boy complained of lower limb pain on the evening before admission, which was treated with dipyrone. He had received the Pfizer-BioNTech BNT16B2b2 mRNA COVID-19 vaccine four days before admission. A fast antigen oropharyngeal swab test for COVID-19 infection returned negative on admission. Blood tests revealed mild microcytic anemia (hemoglobin 11g/dL, hematocrit 32.9%, median corpuscular volume 73.3fL, and median corpuscular hemoglobin 24.5 pg); normal white blood cell count (5.4 x10^9/L, with 54% neutrophils and 33% lymphocytes); platelet count: 274,000; sedimentation rate: 50mm; urea: 26mg/dL; creatinine: 1mg/dL; urine sediment: 5 red blood cells, negative for protein. He was diagnosed with new-onset Henoch-Schönlein purpura, which occurred in close temporal association with the first dose of Pfizer-BioNTech BNT16B2b2 mRNA COVID-19 vaccine. He was treated with prednisolone therapy for seven days, showed improvement (Figure B), and was subsequently discharged. Two weeks after his initial discharge, the patient was readmitted because of recurrent purpuric lesions, pain, and edema on his left wrist and hand. Administration of prednisolone again resulted in regression of the manifestations, and the patient was subsequently discharged. Renal function was monitored for potential complications. Four weeks later, the patient's arterial pressure was measured at 100/70mmHg, and his urine test results were normal. The patient received his second dose of the Pfizer-BioNTech BNT16B2b2 mRNA COVID-19 vaccine on May 12, 2022, with no reported adverse events. Four

104 months after the initial diagnosis of Henoch-Schönlein purpura, the patient's blood
105 pressure was measured at 110/60mmHg. However, on June 13, 2022, the patient's
106 urine sediment revealed 45 red blood cells per field and 1+ proteinuria. The patient's
107 blood pressure and urine test returned to normal one month later.

Discussion

This 6-year-old boy meets the mandatory diagnostic criteria of nonthrombocytopenic purpura and two of the four supporting criteria for Henoch-Schönlein purpura, including arthritis and renal involvement as proteinuria or hematuria [5]. In this child, without underlying or concomitant disease, there was a temporal association between the occurrence of two episodes of the Henoch-Schönlein purpura and administration of the first dose of Pfizer-BioNTech BNT16B2b2 mRNA vaccine COVID-19. New-onset of Henoch-Schönlein purpura events temporally associated with the COVID-19 vaccination were also reported in a 16-year-old girl [6] and an 11-year girl [7], nine days after the first and five days after the second Pfizer-BioNTech BNT16B2b2 mRNA COVID-19 vaccine dose, respectively. In vaccinees with purpura associated with vasculitis, urinalysis and kidney function monitoring is mandatory, as is for patients with a previous glomerular disease (IgA nephropathy or Minimal Change Disease) because of the possibility of aggravation by the immunization with mRNA-based vaccines [8].

Unfortunately, the COVID-19 vaccine events reporting systems are not accurate since there is no expert validation of the episodes. Thus, there are no databases available to extract estimates of side effects. Adults may experience immune-mediated disease flare-ups or new-onset disease after receiving the mRNA/DNA COVID-19 vaccine [9, 10]. On average, events start four days after vaccination, and 75% of cases were mild to moderate in severity. One incidence of Henoch-Schönlein occurred in a 53-year-old patient three days after receiving the first dose of the Pfizer-BioNTech BNT16B2b2 mRNA COVID-19 vaccine. The patient responded quickly to cortisol therapy. In an

assessment of 1,415 cutaneous reactions to the COVID-19 vaccine in adults [11], sixty-one percent of the 41 incidents in 11 observational studies were linked to the administration of the Pfizer-BioNTech BNT16B2b2 mRNA COVID-19 vaccine. Purpuric lesions occurred in 16 of these patients on average 7.6 days after vaccination, lasting 15.7 days.

The observed temporal association between vaccination and the occurrence of rare allergy-like reactions in a few adult vaccinees pointed to the polyethylene glycol-polar lipid conjugate (0.05 mg/dose) in the mRNA carrier nanoparticles as the likely trigger of the hyper reaction, which may or may not be mediated by preexisting antibodies elicited by previous exposure to drugs containing these compounds [12]. Our patient did not have an acute-onset rash despite being treated with polyethylene glycol-containing dipyrone. Therefore, the new-onset of the Henoch-Schönlein purpura in vaccinees is an alert of an underlying autoimmune/inflammatory condition.

Strengths and limitations

This study's strengths include the earliest temporal association of Henoch-Schönlein purpura with a mRNA-based COVID-19 vaccine and the five-month follow-up, demonstrating the resolution of the adverse episode in the child. These findings are noteworthy given that adults typically experience worse clinical courses and outcomes with this condition. However, there are some limitations to our study. We did not perform immunofluorescence staining to confirm IgA deposits in the mesangium of cutaneous tissue, which is the gold standard for diagnosing Henoch-Schönlein purpura. We did not investigate the molecular genetic basis of the patient's Henoch-Schönlein episode, which may have shed more light on the pathogenesis of the disease. Finally, the genetic basis of Henoch-Schönlein is not fully understood, with the human leukocyte antigen (HLA) region, particularly class II alleles such as HLA-DRB1 alleles, being the most strongly associated genetic factor [13].

Concluding remarks

Overall, the data suggest that the benefits of COVID-19 vaccination far outweigh any potential risks, even for children. While isolated cases of Henoch-Schönlein purpura have been reported, they are rare and typically resolve without severe consequences. We encourage all eligible individuals to receive the COVID-19 vaccine to help protect themselves and others from this highly infectious and potentially deadly virus.

166 **Authors´ contributions**

167 Regina Célia de Souza Campos Fernandes and Enrique Medina-Acosta had the idea for
168 the paper.
169 Regina Célia de Souza Campos Fernandes and Enrique Medina-Acosta wrote the paper.
170 Regina Célia de Souza Campos Fernandes, Daniela Vieira Nunes, Nathália Fragoso de
171 Almeida, Nathalia da Cruz Assad Monteiro, Luiza Amanda Maron Pimenta, pediatric
172 specialist, expert clinical observation, and collected data.
173 Regina Célia de Souza Campos Fernandes and Enrique Medina-Acosta conducted the
174 review from Medline and PubMed databases.
175

176 **Data access statement**

177 All patient data are provided in the manuscript

178 **Ethics statement**

179 This study was conducted following the recommendations of the Brazilian National
180 Ethics Committee CONEP with written informed consent from the legal guardian and
181 under the Code of Ethics of the World Medical Association (Declaration of Helsinki) for
182 experiments involving humans. The protocol was approved by the CONEP (national
183 approval registry CAAE no. 35385714.0.0000.5244).

184

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189 decision, or manuscript preparation.

190

191 **Figure legend**

192 Right lower limb purpuric lesions upon admission (A) and post-treatment regression
193 (B)

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Declaration of interest statement

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.